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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/587,681	07/29/2006	Stefano Vassanelli	NBG-116	8469

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EXAMINER	
BOWERS, NATHAN ANDREW	

ART UNIT	PAPER NUMBER
1775	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/587,681	VASSANELLI ET AL.	
	Examiner	Art Unit	
	NATHAN A. BOWERS	1775	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 December 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *4,5 and 7-15* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *4,5 and 7-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)

2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.

4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.

5) ☐ Notice of Informal Patent Application

6) ☐ Other: _____.

DETAILED ACTION

Claim Objections

1) Claim 14 is objected to because of the following informalities: parentheticals are given no patentable weight when evaluating the claimed limitations, and therefore should not be present in the claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was

not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

2) Claims 4, 5, 7-11 and 15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Xu (US 20050112544) in view of Sugihara (US 6132683).

With respect to claim 4, Xu discloses a biochip comprising an array of microelectrodes (Figure 1A:110, 120). Paragraph [0038] indicates that each microelectrode is positioned on a solid substrate. Paragraph [0048] further states that an insulating layer (i.e. silicone-dioxide) is provided on the substrate to form a strip upon which each microelectrode is positioned. Xu additionally teaches in paragraphs [0192] and [0198] that each microelectrode within the array is individually addressed and in communication with a switching system using conductive traces (Figure 1A:130) and conductive pads (Figure 1A:150). Because Xu teaches in paragraph [0147] that each microelectrode structure occupies a size "less than 50 micron by 50 micron," it is understood that each microelectrode may be in communication with only a single cell (especially when the cells of interest are larger than 50 microns in diameter). Paragraphs [0038] and [0040] teach that each microelectrode array is located at the bottom of a cell culture chamber formed by an individual well of a multi-well plate. Accordingly, cells can be grown and adhere in contact with the array of microelectrodes on a surface formed by the insulating layer of the solid substrate. Xu, however does not expressly disclose that two reference electrodes are integrated with the insulating layer of the semiconductor substrate.

Sugihara discloses a similar biochip comprising a substrate (Figure 2:2) upon which a cell culture chamber (Figure 2:6) is formed. A plurality of measuring electrodes (Figure 3:11) and conductive traces (Figure 3:12) are located within the cell culture chamber, as well as at least two electrodes (Figure 4:10) acting as a ground reference. This is described in column 6, line 32 to column 7, line 7.

Xu and Sugihara are analogous art because they are from the same field of endeavor regarding biochips comprising microelectrodes configured to evaluate cells.

At the time of the invention, it would have been obvious to ensure that the Xu biochip included at least two electrodes acting as a ground reference. Sugihara teaches in column 1, lines 49-52 that noise is often a problem when measuring very low level or micro-potentials such as cell potentials. Sugihara indicates in column 2, lines 42-52 the use of multiple reference electrodes serves to lower the impedance of the overall system, which thereby lowers the noise often inherent in the measured data.

With respect to claims 5 and 9, Xu and Sugihara disclose the biochip set forth in claim 4. Additionally, Xu teaches that the substrate serves as a solid support upon which cell culture chambers and microelectrode arrays are formed. See paragraph [0038]. Paragraph [0048] indicates that the substrate is manufactured using dielectric materials such as glass or ceramics. Paragraph [0038] further describes the use of conductive traces (Figure 1A:130) and pads (Figure 1A:150) used to connect each microelectrode to external parallel connectors using wire bonding. Figures 13 and 14 describe how each microelectrode array is in communication with an external printed

circuit board or electronic conductor lines capable of communicating with a switching system and/or an analysis device.

With respect to claim 7, Xu and Sugihara disclose the biochip set forth in claim 5. Furthermore, Xu teaches in paragraphs [0028] and [0048] that the substrate is manufactured from silicon, and that the insulating layer is silicone-dioxide.

With respect to claim 8, Xu and Sugihara disclose the biochip set forth in claim 5. Xu additionally teaches in paragraph [0181] that the substrate is formed using an optically transparent material.

With respect to claim 10, Xu and Sugihara disclose the biochip set forth in claim 5. Xu teaches in paragraph [0147] that each microelectrode may be 1 or 5 microns in width.

With respect to claim 11, Xu and Sugihara disclose the biochip set forth in claim 4. Xu further discloses in paragraph [0038] that the microelectrodes are constructed from electrically conductive materials.

With respect to claim 15, Xu and Sugihara disclose the apparatus in claim 11 as set forth in the 35 U.S.C. 103 rejections above. As previously described, Xu discloses capacitive metal microelectrodes (Figure 1A:110, 120) positioned on a glass, ceramic

and/or silicon substrate in communication with an insulating layer (i.e. silicone-dioxide). Xu, however, does not expressly state that a passivation layer is provided on non-exposed areas between microelectrodes.

Sugihara discloses the apparatus as previously described above. Sugihara additionally indicates in column 7, lines 19-27 that an insulating film (Figure 5:14) is provided between microelectrodes (Figure 5:11). The insulating film covers areas of the conductive trace (Figure 5:12) that are not exposed by the microelectrodes.

At the time of the invention, it would have been obvious to provide an insulating passivation layer between each of the Xu microelectrodes. Sugihara indicates in column 7, lines 19-27 that it is possible to apply an insulating film in precise locations using known micromachining techniques. One of ordinary skill would have recognized an insulating passivation layer to be beneficial because it would serve to electrically isolate each microelectrode and thereby improve measurement accuracy.

3) Claims 4, 5, 7-11 and 15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Xu (US 20050112544) in view of Sugihara (US 6132683) and Johnson (US 7521224).

Xu and Sugihara disclose the combination set forth in the rejections above. As previously asserted, the Xu is considered to be fully capable of being operated such that each microelectrode is connected to a single cell. For the sake of argument and in order to expedite prosecution, if it is later determined that Xu does not disclose a

structure wherein each electrode may be connected to a single cell, Xu fails to anticipate the claims.

Johnson, however, discloses that it is known in the art to provide a microelectrode structure wherein specific electrode structures (Figure 2:212 and Figure 2:213) are assigned to promote the poration of a specific cell (Figure 2:214). This is described in column 4, lines 25-50.

Xu and Johnson are analogous art because they are from the same field of endeavor regarding electroporation arrays.

At the time of the invention, it would have been obvious to ensure that each individually addressable microelectrode structure disclosed by Xu is capable of being connected with only a single cell. Johnson teaches that this configuration is beneficial because it allows one to monitor the varying effects of a drug or other substance on a plurality of cells that are simultaneously exposed to different electroporation conditions. One of ordinary skill would have recognized that only minor structural alterations would be necessary in order to use the electrode array of Xu to test cells on an individual basis.

4) Claim 12 is rejected under 35 U.S.C. 103(a) as being unpatentable over Xu (US 20050112544) in view of Sugihara (US 6132683) as applied to claim 11, and further in view of Casnig (US 5134070).

Xu and Sugihara the apparatus in claim 11 as set forth in the 35 U.S.C. 103 rejections above. As noted in the previous rejections above, Xu teaches the use of

conductive microelectrodes and traces obtained over a silicon substrate covered with a silicone-dioxide insulating layer. Xu additionally teaches in paragraph [0179] that the electrodes and traces are constructed from metals such as aluminum and gold. Paragraph [0180] indicates that the electrodes and traces are formed by overlaying (i.e. "sandwiching") conductive films that each comprise a different conductive metal. Xu, however, does not disclose the use of titanium nitride as an electrode trace material.

Casnig discloses a cell culture container comprising a substrate (Figure 3:1) coated with a metal distribution electrode (Figure 3:3). Column 7, line 59 to column 8, line 49 further teaches that a gold thin film (Figure 4:24) and a titanium nitride coating (Figure 4:2) are additionally provided on the substrate.

Xu and Casnig are analogous art because they are from the same field of endeavor regarding devices for culturing cells on electrode surfaces.

At the time of the invention, it would have been obvious to form the conductive traces of Xu overlaying titanium nitride, aluminum and gold layers. As evidenced by Casnig, titanium nitride is a biocompatible and conductive material well suited for use as an electrode in an apparatus designed to subject a cell culture to an electrical field. Casnig teaches in column 8, lines 31-49 that titanium nitride exhibits desirable qualities relating to chemical/mechanical stability, biological inertness and cost, and is an appropriate material to facilitate cell adhesion.

5) Claims 13 and 14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Xu (US 20050112544) in view of Sugihara (US 6132683) as applied to claim 11, and further in view of Gomez (US 20030157587).

Xu and Sugihara disclose the apparatus in claim 11 as set forth in the 35 U.S.C. 103 rejections above. As noted in the rejections above, Xu additionally teaches in paragraph [0179] that the electrodes and traces are constructed from metals such as aluminum and gold, and are in communication with metal contact plugs and pads (Figure 1A:150). Xu, however, does not expressly disclose the that microelectrodes are formed using MOS technology.

Gomez discloses a silicon wafer biochip (Figure 1:22) comprising an array of microelectrodes (Figure 1:36) designed to detect an analyte (such as a cell or biomolecule) in solution by measuring impedance. This is set forth in paragraph [0087]. Paragraphs [0147] and [0148] further indicate that the detection electrodes are formed by attaching binding agents to the gate of a silicon MOSFET. MOSFET structures inherently comprise a silicon p-type substrate comprising n-doped regions, a drain, a source and a gate.

Xu and Gomez are analogous art because they are from the same field of endeavor regarding biochip devices comprising microelectrodes configured to measure cell impedance.

At the time of the invention, it would have been obvious to form the electrodes of Xu in communication with MOS transistors. Gomez teaches in paragraphs [0147] and [0148] that MOSFET structures are commonly used in microfluidic biochips with an

electrode array to provide an electrical field capable of stimulating and analyzing cells. MOSFET transistors are considered to be very common transistors because they are easily micromachined and highly dependable. Accordingly, one of ordinary skill would have been able to achieve predictable results using MOS technology to construct the microelectrodes of Xu.

6) Claim 12 is rejected under 35 U.S.C. 103(a) as being unpatentable over Xu (US 20050112544), Sugihara (US 6132683) and Johnson (US 7521224) as applied to claim 11, and further in view of Casnig (US 5134070).

Xu, Sugihara and Johnson disclose the apparatus in claim 11 as set forth in the 35 U.S.C. 103 rejections above. As noted in the previous rejections above, Xu teaches the use of conductive microelectrodes and traces obtained over a silicon substrate covered with a silicone-dioxide insulating layer. Xu additionally teaches in paragraph [0179] that the electrodes and traces are constructed from metals such as aluminum and gold. Paragraph [0180] indicates that the electrodes and traces are formed by overlaying (i.e. "sandwiching") conductive films that each comprise a different conductive metal. Xu, however, does not disclose the use of titanium nitride as an electrode trace material.

Casnig discloses a cell culture container comprising a substrate (Figure 3:1) coated with a metal distribution electrode (Figure 3:3). Column 7, line 59 to column 8, line 49 further teaches that a gold thin film (Figure 4:24) and a titanium nitride coating (Figure 4:2) are additionally provided on the substrate.

Xu and Casnig are analogous art because they are from the same field of endeavor regarding devices for culturing cells on electrode surfaces.

At the time of the invention, it would have been obvious to form the conductive traces of Xu overlaying titanium nitride, aluminum and gold layers. As evidenced by Casnig, titanium nitride is a biocompatible and conductive material well suited for use as an electrode in an apparatus designed to subject a cell culture to an electrical field. Casnig teaches in column 8, lines 31-49 that titanium nitride exhibits desirable qualities relating to chemical/mechanical stability, biological inertness and cost, and is an appropriate material to facilitate cell adhesion.

7) Claims 13 and 14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Xu (US 20050112544), Sugihara (US 6132683) and Johnson (US 7521224) as applied to claim 11, and further in view of Gomez (US 20030157587).

Xu, Sugihara and Johnson disclose the apparatus in claim 11 as set forth in the 35 U.S.C. 103 rejections above. As noted in the rejections above, Xu additionally teaches in paragraph [0179] that the electrodes and traces are constructed from metals such as aluminum and gold, and are in communication with metal contact plugs and pads (Figure 1A:150). Xu, however, does not expressly disclose the that microelectrodes are formed using MOS technology.

Gomez discloses a silicon wafer biochip (Figure 1:22) comprising an array of microelectrodes (Figure 1:36) designed to detect an analyte (such as a cell or biomolecule) in solution by measuring impedance. This is set forth in paragraph [0087].

Paragraphs [0147] and [0148] further indicate that the detection electrodes are formed by attaching binding agents to the gate of a silicon MOSFET. MOSFET structures inherently comprise a silicon p-type substrate comprising n-doped regions, a drain, a source and a gate.

Xu and Gomez are analogous art because they are from the same field of endeavor regarding biochip devices comprising microelectrodes configured to measure cell impedance.

At the time of the invention, it would have been obvious to form the electrodes of Xu in communication with MOS transistors. Gomez teaches in paragraphs [0147] and [0148] that MOSFET structures are commonly used in microfluidic biochips with an electrode array to provide an electrical field capable of stimulating and analyzing cells. MOSFET transistors are considered to be very common transistors because they are easily micromachined and highly dependable. Accordingly, one of ordinary skill would have been able to achieve predictable results using MOS technology to construct the microelectrodes of Xu.

Response to Arguments

Applicant's arguments filed 27 December 2010 with respect to the 35 U.S.C. 102 and 35 U.S.C. 103 rejections involving Xu have been fully considered but they are not persuasive.

Applicant's principle arguments are

(a) Xu discloses paired electrodes being driven as pairs and addressed as pairs. Accordingly, Xu does not teach that each microelectrode is selectively/individually driven.

In response, please consider the following remarks.

It is agreed that each well of Xu contains a pair of microelectrodes. However, the microelectrodes provided in each well are independently driven from one another, as each electrode structure is coupled to a separate bus and connection pad. The first electrode of each electrode pair is operated as a driving electrode to generate an electric field within the well. The second electrode of each electrode pair is operated as a sensing electrode to measure a change in impedance produced by cell(s) on the substrate.

(b) Xu does not disclose a plurality of microelectrodes, wherein each microelectrode is connected to a single cell.

In response, please consider the following remarks.

As described in the rejections above, Xu discloses in paragraph [0147] a microelectrode structure characterized by a size and geometry that would potentially allow each microelectrode to be connected to a single cell. For example, Xu discloses individual electrodes as small as 5 microns in length and width. It is very likely that, an electrode of this size would be covered by only a single cell (especially an animal cell).

(c) Xu and Sugihara do not disclose reference electrodes positioned outside of a defined array region occupied by the array of microelectrodes.

In response, please consider the following remarks.

As described in the rejections above, Sugihara discloses in at least in column 6, line 32 to column 7, line 7 that a plurality of electrodes (Figure 4:10) serve as a ground reference. From Figure 4, it is apparent that these reference electrodes are on the same plane as the electrode detection array, and are offset from the electrode detection array.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to NATHAN A. BOWERS whose telephone number is (571) 272-8613. The examiner can normally be reached on Monday-Friday 7 AM to 4 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Marcheschi can be reached on (571) 272-1374. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Nathan A Bowers/
Primary Examiner, Art Unit 1775